Kidney International, Vol. 17 (1980), pp. 571–576

EDITORIAL REVIEW

Symptomatic hypotension during hemodialysis

Symptoms during treatment with extracorporeal hemodialysis are an unpleasant fact of life maintained by the artificial kidney. During hemodialysis, a common clinical pattern is dizziness, malaise, nausea, and cramps accompanied by a fall in blood pressure, requiring some form of therapeutic intervention by the nurse or technical team. Such symptomatic hypotension occurs in approximately 25% of hemodialysis treatments. For some patients, symptomatic hypotension recurs frequently enough to make maintenance dialysis a nightmare. This review is an effort to fit into some kind of reasonable pathophysiologic schema the large body of information on symptomatic hypotension.

Vascular volume depletion

"Dry weight" for a given patient is frequently defined as the weight obtained at the conclusion of a regular dialysis treatment below which the patient more often than not will become symptomatic and go into shock. Clinical wisdom quite properly relates symptomatic hypotension not only to the *amount* of ultrafiltrate taken during hemodialysis treatment (net negative fluid balance) but also to the *rate* at which the removal occurs. Shear et al demonstrated the rather constant rate of reabsorption of fluid from the peritoneal space [1–3]. We may reasonably extrapolate from the capillaries of the splanchnic bed to capillaries throughout the body and argue that each patient has a finite rate of recruitment of fluid from the extravascular into the vascular space and that if removal of plasma water by the artificial kidney exceeds that rate for long enough, hypovolemic shock with its attendant symptoms will occur. The logic of shock occurring when ultrafiltration sufficiently depletes the vascular volume is undeniable but overly simplistic in the setting of maintenance dialysis for chronic uremia. It should be recognized that vascular volume may be partitioned into intrathoracic and peripheral "compartments." To date, no studies address changes in these compartments with artificial kidney treatment. In addition, Bergström et al [4, 5], Schuenemann et al [6], Rouby et al [7], and Rodrigo et al [8] recently have called attention to the importance of osmolar changes occurring during dialysis therapy. Consider the common circumstance where 1 to 3 liters of plasma water are removed over a 4-hour period. During the course of that removal, plasma proteins are concentrated, providing an enhanced oncotic force to recruit extravascular fluid into the vascular space. This force when quantitated in terms of milliosmoles per liter would seem to be trivial at best, as it would provide less than $^1/_2$ mOsm (that is, < 10 mm Hg) driving gradient for capillary water reabsorption. This, however, is quite sufficient to unbalance the Starling forces of the microcirculation in favor of reabsorption of extravascular fluid. Consider further, that the small, more osmotically active solutes urea and creatinine move from blood into the dialysis bath. Urea and creatinine at steady state are presumed to be in diffusion equilibrium with intracellular water. With the abrupt reduction of the plasma water concentration of these solutes during dialysis and the lag in equilibration across biologic membranes, then an additional osmotic driving gradient for cell uptake of water would occur, leaving the extracellular space to be refilled from the already diminished intracellular space. For a given ultrafiltration rate, the magnitude of this volume depletion would clearly be a direct function of the rate of fall in plasma urea concentration with dialysis. "High efficiency" dialyzers, especially when used in the clinical setting of a high plasma urea nitrogen, would then put the patient at greater risk for symptomatic hypotension than would less efficient (smaller area) dialyzers or peritoneal dialysis, where the urea clearance rate is less [9–13].[1] Further, dialyzers with large

[1]Dialyzers with a greater than 1.0 m^2 of membrane area and with a urea clearance at 200 ml/min blood flow rate of $\geq$ 150 ml/min (range 150 to 180 ml/min) are considered to be high efficiency when compared with more standard equipment where urea clearances of 120 ml/min are common.

Received for publication April 20, 1979
and in revised form August 7, 1979

0085-2538/80/0017-0571 $01.20

surface areas offer the potential for shorter treatment periods, and hence, the fluid removal required to maintain the patient "dry" must be accomplished in this shorter treatment time, accentuating the problem of symptomatic hypotension. These pathophysiologic speculations have recently been tested and found to be valid [7, 14].

From this pathophysiologic schema, we may then examine the observation by Bergström and others that if ultrafiltration is conducted separately in time from diffusional solute loss, that symptomatic hypotension is less frequent. By separating ultrafiltration with its resulting increase in oncotic force from diffusional urea removal, we may speculate that there is but a single force depleting the vascular volume (ultrafiltration) and that this is partially offset by the enhanced oncotic force recruiting extravascular volume. Note that all empirical therapies offered for symptomatic hypotension (hypertonic mannitol, isotonic and hypertonic saline and plasminate) provide an extracellular solute particle with osmotic or oncotic capability to recruit vascular volume.

The data obtained on cardiac output and peripheral vascular resistance of uremic patients undergoing hemodialysis bear comment. The studies in humans by Wehle et al [15], Hampl et al [16], and Chen et al [17] using both invasive and noninvasive methods and the studies in dogs by Keshaviah et al [14] showed a failure of peripheral resistance to increase appropriately with fluid removal during conventional hemodialysis. In addition, heart rate (and cardiac output) failed to increase, as noted by others using noninvasive techniques to assess these autonomic nervous system compensatory mechanisms. Compensatory peripheral vasoconstriction with fluid removal was better maintained with both sequential filtration and dialysis [15] and hemofiltration [16] than it was for hemodialysis. Although these findings add a further level of understanding to the pathophysiologic events leading to symptomatic hypotension, the underlying cause for the differences noted remains obscure. We may speculate that the functional "lesion" identified is the result of an acute vasculopathy or autonomic neuropathy mediated by an osmotic fluid shift that results in failure of the afferent and efferent resistances of the microvasculature to constrict appropriately when fluid is removed from the vascular space.

Physicochemical toxicity

The work of Graefe et al [12] and Novello et al [18] in humans and that of Keshaviah et al [14] and Kirkendol et al [19] in animals suggest the importance of acetate as an etiologic agent for symptomatic hypotension in certain instances. The rate at which acetate may be metabolically disposed of varies from patient to patient. Symptomatic hypotension occurs in those where the rate of acetate uptake from the treatment exceeds its rate of metabolism in the tissues and a significant level of acetate develops in the blood. Kishimoto et al [20], studying 27 patients treated with an acetate bath, showed that serum acetate concentrations in those with symptomatic hypotension (56% of 102 dialyses) had an average serum acetate concentration of 4.5 ± 1.2 mmoles/liter as compared with a concentration of 1.4 ± 0.5 mmoles/liter ($P < 0.005$) for those who were free of this complication. High efficiency dialysis again predisposes toward higher plasma acetate concentrations. The precise mechanism for acetate's action is still unclear; that is, is it cardiotoxic, or is the toxicity primarily at the microcirculatory level with venular pooling secondarily compromising cardiac output? Or both?

Autonomic neuropathy

Classical compensatory cardiovascular mechanisms protect us from changes in vascular volume. Carotid, aortic, and cardiopulmonary baroreceptors sense a depletion in arterial vascular volume. In compensation, an increase in both cardiac output and peripheral vascular resistance occurs in an effort to hold blood pressure stable. Autonomic insufficiency has been noted in the patient with end-stage renal failure by several groups [21–27]. Lilley, Golden, and Stone implicate the carotid and aortic body baroreceptor reflex arc as being defective in a subset of the uremic population [26]. Their data suggest a defect that lies in the afferent limb and may be anywhere along its path; that is, the baroreceptors themselves, the baroreceptor nerve, or its central connections in the medulla. Typical clinical findings in this group were hypertension, lability of blood pressure as clinically manifest by the usual presence of symptomatic hypotension when fluid was removed during routine clinical hemodialysis, and a significantly higher plasma dopamine-β-hydroxylase (DBH) activity. Total peripheral resistance in these patients was not measured, but it has been shown by others to be high when corrected for the low hematocrit typically present with chronic uremia [28, 29]. Patients demonstrating baroreceptor reflex arc dysfunction show findings similar to animals in which surgical section of the afferent nerve from the baroreceptors has been performed [30–33].

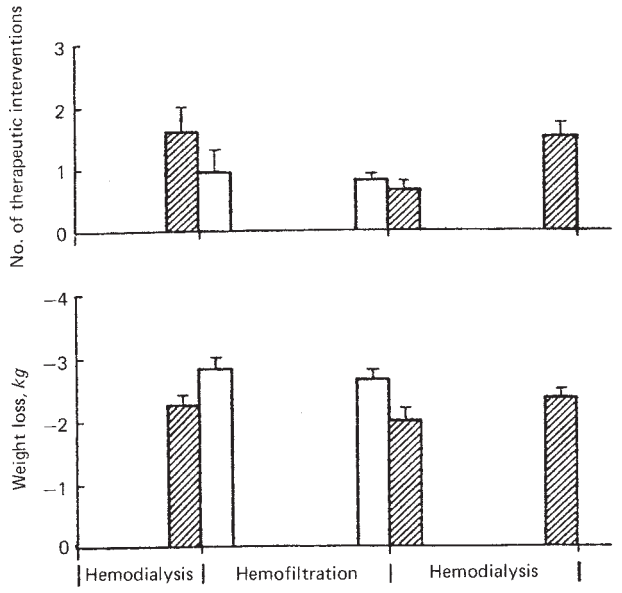

Fig. 1. *Time course in 11 patients for the improvement in symptoms requiring treatment.* Each *bar* represents the mean value for the number of therapeutic interventions recorded by the nurse for ten treatments. The number of interventions noted for the first and last ten hemofiltration treatments is significantly different from the first and last ten hemodialysis treatments ($P < 0.05$). The first ten treatments on return to hemodialysis after hemofiltration also show this significant improvement. Weight loss during hemofiltration is significantly greater than it is with hemodialysis ($P < 0.01$).

These animals are hypertensive, have a high total peripheral resistance resulting from unopposed sympathetic nervous system activity, and lability of blood pressure in response to sodium and volume loading.

DBH is a presynaptic enzyme that catalyzes the last step in the series of reactions leading to the synthesis of norepinephrine. It is secreted into the plasma on a mole-for-mole basis with norepinephrine. DBH, when contrasted with norepinephrine, is not readily degraded biochemically or eliminated at all from the plasma by reuptake by the nerve ending or loss in the urine. Hence, DBH has a substantially longer half life in the plasma than does norepinephrine [31, 34, 35]. It is considered by many to reflect a longer-term (days) level of activity of the sympathetic nervous system more closely than does plasma norepinephrine concentration, which reflects the more acute (minute to minute) peak and valley swings in activity. Elevation of plasma DBH activity then may be considered as additional supporting evidence for an excess of sympathetic nervous system "tone."

I have studied a small group of patients with end-stage renal disease undergoing hemofiltration. They were selected only because they had significant hypertension [36]. In a crossover protocol where hemofiltration was compared with bracketing control observations, half responded to hemofiltration with a significant reduction in mean arterial pressure after 3 months time on treatment. Changes of the mean arterial pressure to sodium and volume loading (that is, the changes in mean arterial pressure between that measured at the end of one treatment and prior to initiating the next [ΔMAP]) were taken as an index of blood pressure lability. Those who showed a reduction in mean arterial pressure also showed both a reduction of ΔMAP and plasma DBH activity [36, 37]. Furthermore, a significant reduction in the frequency of symptomatic hypotension during treatment was noted with hemofiltration [38–40]. With return to hemodialysis, mean arterial pressure, ΔMAP, and plasma DBH activity returned to control values within 3 months, as did the incidence of symptomatic hypotension. The findings of decreased blood pressure and blood pressure lability suggest improved baroreceptor reflex arc function as a result of hemofiltration.[2] Normalization of blood pressure and a reduced number of episodes of symptomatic hypotension have subsequently been noted by other groups [43, 44].

Figure 1 plots the number of therapeutic interventions per treatment with the artificial kidney for hemofiltration and hemodialysis in our study. Weight reduction per treatment is also plotted. A significant reduction in the need for therapy is noted with hemofiltration. The time course for the reduction in number of episodes of symptomatic hypotension, when compared with that for the reduction in mean arterial pressure, and ΔMAP showed that improvement in symptomatic hypotension occurs with the very first ten hemofiltration treatments undertaken, whereas the other findings were manifest on-

[2]The complex problem of baroreceptor function and high blood pressure has received a lot of attention since 1923 when Hering first discovered the carotid sinus reflex and postulated that a derangement of this reflex might cause hypertension. I do not intend to offer a full review of this information. Suffice it to say that present thinking [41] indicates that a resetting of the level of the "servo point," around which the reflex modulates changes in blood pressure, occurs at a higher level in nonuremic patients with hypertension. Whether hypertension or "resetting" is the first event is not clear. Further, it is not clear whether reflex sensitivity (gain) is blunted by moderate hypertension. Last, studies to determine reflex resetting and altered sensitivity in patients with renal failure and hypertension are few [23–27]. They indicate, primarily, a reduction in sensitivity of the mechanisms involving baroreceptor pulse interval regulation. In addition, although data from Kersh et al [25] suggest a normal end-organ responsiveness to catecholamine, Romoff et al have data to suggest end-organ unresponsiveness [42].

ly in the last 4 to 6 weeks of the 3-month study period on hemofiltration [39]. This occurred in spite of greater weight loss during treatment with hemofiltration than with hemodialysis. Furthermore, on return to hemodialysis, the lowered incidence of symptomatic hypotension persisted for the first ten treatments, but it rose to prehemofiltration control levels in the last 4 to 6 weeks of the concluding control period (see Fig. 1). The different time course noted for the reduction in symptomatic hypotension, as opposed to reduction in MAP and ΔMAP, raises several points of interest. First, it indicates that there are at least two pathophysiologic mechanisms underlying the reduction in symptomatic hypotension noted with hemofiltration. One, because of its abrupt onset, may well relate to a technical difference between hemofiltration and hemodialysis (for example, the less efficient removal of urea and creatinine and the presentation of more acetate with hemofiltration than for hemodialysis or the use of a different [noncellulosic] membrane[3]). The other, with its slow course of onset that persists on return to hemodialysis, suggests a biological rather than a technical event (for example, improved removal of a slowly accumulating middle molecule that inhibits one or another component of the afferent limb of the baroreceptor reflex arc with subsequent restoration towards normal of the hemodynamic responses to vascular volume reduction). Of interest is a preliminary report from Shaldon et al [45] in which changes in osmolality and in posttreatment acetate concentrations were comparable during hemofiltration and hemodialysis in a small group of patients who showed the prompt and significant reduction in symptomatic hypotension noted in Fig. 1. If acetate toxicity and alterations in osmolar and oncotic relationships are excluded in the explanation of the early component of improvement in symptomatic hypotension, more emphasis is placed on differences in the membrane used.

Membrane toxicity

Cellulosic membrane clearly triggers surface sensitive proteins discharging the complement cascade. This, in turn, relates temporally to the pulmonary sequestration of leukocytes early in the course of cellulosic hemodialysis [46–51]. Some feel this leukocyte sequestration may underly the fall in arterial partial pressure of oxygen (P_aO_2) noted with hemodialysis [50, 51]. The dissociation between leukocyte sequestration and a reduction in P_aO_2 casts doubt, however, on this as the etiologic mechanism [52]. Amicon XM-50 membrane has been contrasted closely with the regenerated cellulose acetate membrane from Dow and found not to cause such leukocyte sequestration or to perturb inherent leukocyte function such as random mobility, phagocytosing ability, or response to a chemotactic stimulus, unlike the Dow membrane [49]. The closely related XP-50 membrane from Amicon now commonly being used for hemofiltration also does not cause hemodialysis leukopenia (Henderson, unpublished observations), nor does AN-69 polyachrilonitrile membrane from Rhone Poulenc, although the latter does trigger complement [54]. To date, no prospective studies have been reported to test the hypothesis that cellulosic membrane toxicity may be responsible for some of the symptomatic hypotension noted during hemodialysis.

Table 1. Potential causes for symptomatic hypotension during dialysis

1. Osmotic/oncotic derangements of vascular volume
2. Uremic autonomic neuropathy
3. Toxicity of acetate
4. Toxicity of cellulosic membrane
5. Other

What may we conclude from all of this? *First,* symptomatic hypotension is multifactorial. Table 1 lists the significant factors derived from my perception of the literature. Note that items 4 and 5 are purely speculative. *Second,* different patients may well show different patterns of clinical response to treatment, depending on which factor or factors may predominate at the time of treatment. This might reconcile some of the conflicting information in the literature, for example, the findings of Bergström et al with others studying sequential ultrafiltration and hemodialysis. *Third,* any study undertaken to identify cause and effect relationships between symptoms and treatment method must address all of these potential variables. Our understanding of symptomatic hypotension is of utmost importance for the patient, as rational therapy can only be offered after the pathophysiologic mechanisms for its occurrence are understood.

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[3]Two membranes have been most widely used for hemofiltration: the Rhone Poulenc RP-6 polyachrilonitrile membrane and the Amicon XP-50 anisotropic polysulfone membrane.

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